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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,855	10/13/2000	Chaitan Khosla	286002021100	6952
25225	7590	04/21/2004	EXAMINER	
MORRISON & FOERSTER LLP 3811 VALLEY CENTRE DRIVE SUITE 500 SAN DIEGO, CA 92130-2332			KERR, KATHLEEN M	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/687,855

Applicant(s)

KHOSLA ET AL.

Examiner

Kathleen M Kerr

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 28 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1,55,56,58-61,63-69 and 71-83 is/are pending in the application.
- 4a) Of the above claim(s) 75-83 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 61 and 63-68 is/are allowed.
- 6) ☒ Claim(s) 1,55,56,58-60,69 and 71-74 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Application Status***

1. In response to the previous Office action on the merits, a non-Final rejection (mailed on September 26, 2003), Applicants filed an amendment and response received on January 28, 2004. Said amendment cancelled Claims 53, 54, 62, and 70, amended Claims 1, 55, 58, 61, 63, 66, 67, 69, 71 and 72, and added new Claims 78-83. Thus, Claims 1, 55-56, and 58-61, 63-69, and 71-83 are pending in the instant Office action.

### ***Election***

2. For the previous restriction requirement, see the paper mailed on January 24, 2002. New Claims 78 and 81 are restricted into non-elected Group II; new Claims 79 and 82 are restricted into non-elected Group III. New Claims 80 and 83 seem to have an improper dependence and should depend from either Claims 78 and 81 or Claims 79 and 82, respectively. In either event, Claims 80 and 83 do not fall within the elected invention. Thus, Claims 75-83 are withdrawn from further consideration as non-elected inventions. Claims 1, 55-56, 58-61, 63-69, and 71-74 will be examined herein.

### ***Priority***

3. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application Nos. 60/159,090 filed on October 13, 1999, 60/206,082 filed on May 18, 2000 and 60/232,379 filed on September 14, 2000. The following is a summary of the earliest effective filing dates on a claim-by-claim basis considering the examined claims:

May 18, 2000	Claims 1, 55, 56, 58-60, 66, 72
September 14, 2000	Claims 61, 63-65, 67-69, 71, 73-74

***Withdrawn - Objections to the Specification***

4. Previous objection to the specification for citing outdated U.S. patent application numbers is withdrawn by virtue of Applicants' amendment.

***Withdrawn - Claim Rejections - 35 U.S.C. § 112***

5. Previous rejection of Claims 1, 53-55, 58-60, and 69-73 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "phosphopantetheinyl transferase" is withdrawn by virtue of Applicant's amendment inserting functional language to describe the term in the claim.
6. Previous rejection of Claim 54 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicant's cancellation of said claim.
7. Previous rejection of Claim 58 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "disabled" is withdrawn by virtue of Applicant's amendment removing the term.
8. Previous rejection of Claim 66 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "the mat gene" having improper antecedent basis is withdrawn by virtue of Applicant's amendment.
9. Previous rejection of Claim 67 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "the PKS" having no antecedent basis is withdrawn by virtue of Applicant's amendment.

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10. Previous rejection of Claim 72 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “the mat gene” having improper antecedent basis is withdrawn by virtue of Applicant’s amendment.

11. Previous rejection of Claims 61, 64-69, and 72-74 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicants’ amendment to said claims removing use of matB alone.

12. Previous rejection of Claim 58 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicants’ amendment.

***Maintained - Claim Rejections - 35 U.S.C. § 112***

13. Previous rejection of Claims 1, 55, 58-60, and 69-74 under 35 U.S.C. § 112, first paragraph, written description, is maintained in the part pertaining to the written description of phosphopantetheinyl transferases only, all remaining issues of written description related to the instant rejection as previously set forth are herein withdrawn by virtue of Applicants’ amendment to host cells comprising specific sequences, not genera of sequences. See also withdrawal of rejection for the phosphopantetheinyl transferase issue in Claim 56.

Applicants’ arguments with respect to the written description of phosphopantetheinyl transferases in the instant claims have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the amended claims further define phosphopantetheinyl transferases and, thus, have addressed the issue. The Examiner disagrees.

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As previously noted, the specification describes phosphopantetheinyl transferases by noting said transferases in USPN 6,579,695 (see page 5, lines 10-16); it is known that USPN 6,258,566 also teaches said transferases as well. However, not all structural homologs of phosphopantetheinyl transferases in the art phosphopantetheinylate PKSs as evidenced by the fact the *E. coli* o195 protein has little phosphopantetheinylation activity and *E. coli* ACPS has none as shown in USPN 6,579,695 and USPN 6,258,566, respectively. The claims, as amended most recently, are drawn to phosphopantetheinyl transferases that phosphopantetheinylate PKSs; however, the specification does not describe, except by function, this subgenus of phosphopantetheinylating enzymes since no structural reasons are presented in either the instant application or USPN 6,579,695 so that one of skill in the art could recognize the subgenus claimed. Thus, the instant rejection is maintained for Claims 1, 53-55, 58-60, and 69-74.

***Withdrawn - Claim Rejections - 35 U.S.C. § 102***

14. Previous rejection of Claims 61, 62, 64, 65 and 67-68 under 35 U.S.C. § 102(b) as being anticipated by Kao *et al.* is withdrawn by virtue of Applicants' amendment.

**NEW ISSUES**

***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claim 58 is rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which

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was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While the concept of deleting the *E. coli* prpA-D operon is clearly set forth in Examples 2 and 4 of the instant specification, not expressing said operon is not clearly supported in the specification as originally filed. On page 5 of the specification, disabling the operon is mentioned; however, no specific means of disabling is described. No other mention of removal of the prpA-D operon is noted in the specification. Applicants must delete the new matter or cite clear support (page and line number) in the specification as originally filed.

### ***Claim Rejections - 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. Claims 1, 55, 56, 59, and 60 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Santi *et al.* (USPAP 2002/0142401) and Barr *et al.* (WO 98/27203). The instant claims are drawn to modified *E. coli* host cells having *S. coelicolor* pccB and accA2 genes and having expression systems for (1) *B. subtilis* sfp, a phosphopantetheinyl transferase (ppt), (2) *E. coli* birA, a biotin ligase, and (3) DEBS.

Santi *et al.* teach heterologous *E. coli* host cells that overexpress *S. coelicolor* pccB and accA2 genes and birA (see pages 11 and 21 of priority document 60/161703 filed on October 27, 1999) for the purpose of increasing the presence of precursors on the host cell for the efficient

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production of polyketides. Heterologous expression of DEBS genes for the production of erythromycins is also taught (see introductory sections). Santi *et al.* do not teach co-expression of *sfp* in the *E. coli* host cells for the production of polyketides.

Barr *et al.* teach the co-expression of heterologous PKS genes and a holo-ACP synthase, such as *sfp* from *B. subtilis*, for the expression of polyketide-producing polyketide synthases in *E. coli*.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Santi *et al.* and Barr *et al.* to produce *E. coli* host cells that are efficient at polyketide production from recombinantly expressed polyketide synthases because both Santi *et al.* and Barr *et al.* are disclosures of efficient polyketide producing host cells, such as *E. coli*. One would have had a reasonable expectation of success that the above combination would be productive since there is no indication in the art of counterproductive effects of combining propionyl CoA carboxylase and a holo ACP synthase like *sfp*.

### ***Summary of Pending Issues***

17. The following is a summary of the issues pending in the instant application:
- a) Claims 1, 55, 58-60, and 69-74 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
  - b) Claim 58 stands rejected under 35 U.S.C. § 112, first paragraph, new matter.
  - c) Claims 1, 55, 56, 59, and 60 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Santi *et al.* (USPAP 2002/0142401) and Barr *et al.* (WO 98/27203).



***Allowable Subject Matter***

18. The instant claims are drawn to host cells genetically engineered for increased and/or effective polyketide production from recombinantly expressed polyketide synthases (PKSs). *Streptomyces* naturally produce polyketides (by means of polyketide synthases encoded on endogenous PKS genes) while *E. coli* do not, and recombinantly expressed PKS genes effectively produce polyketides in *Streptomyces* but not in *E. coli*, presumably due to some missing “factor(s)” in a non-polyketide-producing host cell. This “factor” has been identified as certain phosphopantetheinyl transferases (see Barr *et al.* WO 98/27203 and Lambalot *et al.* USPN 6,579,695).

While the art is replete with examples of recombinant host cells engineered for polyketide production (see, for example *Streptomyces coelicolor* CH999 cells taught by Khosla *et al* in USPN 5,830,750 whose endogenous PKS gene cluster is deleted wherein new PKS gene clusters can be transformed and productive), fewer are the examples of improving this engineering. Stassi *et al.* teach that the heterologous expression of a recombinant modular PKS in *Saccharopolyspora erythraea* requires the addition of butyryl-CoA, in the form of media supplementation or by means of co-expression of recombinant crotonyl-CoA reductase, which catalyzes the production of butyryl-CoA. While *Rhizobium trifoli* matBC genes are known in the prior art to encode proteins having malonyl-CoA synthetase and dicarboxylate carrier protein activities, no indication of expressing said genes in *Streptomyces* or *E. coli* is found in the prior art. Additionally, *S. coelicolor* matBC genes are also known in the prior art (see specification page 6 and GenBank Accession Number AL163003); however, the prior art only discloses sequence and does not indicate any reason to overexpress matBC in *Streptomyces* or *E. coli*.

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While expression of matA, malonyl-CoA decarboxylase, is indicated in Santi *et al.* (USPAP 2002/0142401) and very generally linked to *S. erythreus* in An *et al.*, no link to matBC is made.

### ***Conclusion***

19. Claims 61 and 63-68 are allowable. Claims 1, 55, 56, 58-60, 69, and 71-74 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

This Office action is **non-final** based on the new ground of rejection (the new 103 rejection).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr  
Examiner  
Art Unit 1652

April 19, 2004